BIARYL COMPOUNDS HAVING ANTI-INFECTIVE ACTIVITY

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] This application claims the benefit of provisional application Serial No. 60/400,671, filed August 2, 2002, the entire contents of which are incorporated herein by reference.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

[0002] NOT APPLICABLE

REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK.

[0003] NOT APPLICABLE

BACKGROUND OF THE INVENTION

1. FIELD OF THE INVENTION

[0004] This invention relates to aromatic compounds having antibacterial activity and methods for their synthesis and use.

2. DESCRIPTION OF RELATED ART

[0005] The discovery of penicillin and other antimicrobials in the early and mid 20th century generated a period of optimism about the medical profession's ability to treat microbial infections. However, the evolution of drug-resistant microbe strains — with new ones being constantly discovered — has led an appreciation of the continuing need to develop new antimicrobials, preferably ones that are structurally different from extant ones or employ a different mechanism of action.

[0006] Exemplary recent disclosures of new antibacterial compounds include Ge et al., WO 01/74898 (2001); Baird et al., US Application No. 10/132,887, filed Apr. 24, 2002; Bürli et al., US Application No. 10/165,856, filed Jun. 6, 2002; McMinn et al., US Application No. 10/165,433, filed Jun. 6, 2002; Bürli et al., US Application No. 10/165,857, filed Jun. 6, 2002; Bürli et al., US Application No. 10/165,764, filed Jun. 6, 2002. Matsunaga et al., US

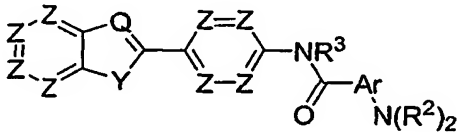
5,821,258 (1998) and US 5,852,011 (1998); and Ohemeng et al., US 5,942,532 (1999) also disclose compounds reportedly having antimicrobial activity.

[0007] Disclosures of compounds that, even though not featured as antimicrobials, have chemical structures that may be relevant to the present invention include Matsunaga et al., US 5,808,087 (1998); JP 11-171886 (1999); and JP 11-189594 (1999); Dykstra et al., US 5,817,686 (1998); Neidle et al., WO 00/63180 (2000); Raspanti, US 5,362,481 (1994); Dantzig et al., WO 97/17069 (1997); Judd, WO 94/11369 (1994); and the IDdb3 database's Drug Report for the drug Phortress (U. Nottingham).

BRIEF SUMMARY OF THE INVENTION

[0008] The present invention provides a compound (I) according to the formula

[0009]



(1)

and the pharmaceutically acceptable salts thereof,

wherein

each Z is independently N or C(R^1), with the proviso that no more than 2 Z's in any one aromatic ring are N;

Y is O, N, or S;

Q is N or C(R^1), with the proviso that Q is C(R^1) when Y is N;

Ar is an aromatic or heteroaromatic 5- or 6-member ring;

each R^1 is independently H, halogen, OH, or a C_1 to C_{12} alkyl or heteroalkyl moiety;

each R^2 is independently H or a C_1 to C_{18} alkyl or heteroalkyl moiety or the two R^2's taken together with the nitrogen atom to which they are attached form a substituted or unsubstituted heteroalkyl 5 to 7 member ring;

and

R^3 is H or a C_1 to C_6 alkyl moiety;

with the proviso that at least one group R^1, R^2, or R^3 contains an alkyl amine group or a quaternary nitrogen group.

[0010] Preferably, the alkylamino group or quaternary nitrogen group is situated in a group R^2.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] Figs. 1 to 14 show synthetic schemes related to the preparation of compounds of this invention.

DETAILED DESCRIPTION OF THE INVENTION

Abbreviations and Definitions

[0012] The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.* C_1-C_{10} means one to ten carbons). Examples of saturated hydrocarbon radicals include groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers.

[0013] The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by $-CH_2CH_2CH_2CH_2-$. Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having six or fewer carbon atoms.

[0014] The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively.

[0015] The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule.

Examples include $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2,-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, and $-CH=CH-N(CH_3)-CH_3$. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by $-CH_2-CH_2-S-CH_2CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied.

[0016] The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include 1 -(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1 -piperazinyl, 2-piperazinyl, and the like.

[0017] The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

[0018] The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon substituent which can be a single ring or multiple rings (up to three rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from zero to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl,

3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

[0019] For brevity, the term "aryl" when used in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

[0020] Each of the above terms (*e.g.*, "alkyl," "heteroalkyl," "aryl" and "heteroaryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

[0021] Substituents for the alkyl, heteroalkyl, aryl, and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be a variety of groups selected from: -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -NH-$C(NH_2)$=NH, -NR'$C(NH_2)$=NH, -NH-$C(NH_2)$=NR', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -CN and -NO_2 in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R" and R"' each independently refer to hydrogen, unsubstituted (C_1-C_8)alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-(C_1-C_4)alkyl groups. When R' and R" are attached to the same nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups such as halo-alkyl (*e.g.*, -CF_3 and -CH_2CF_3) and acyl (*e.g.*, -$C(O)CH_3$, -$C(O)CF_3$, -$C(O)CH_2OCH_3$, and the like). Preferably, the substituted alkyl and heteroalkyl groups have from 1 to 4 substituents,

more preferably 1, 2 or 3 substituents. Exceptions are those perhalo alkyl groups (e.g., pentafluoroethyl and the like) which are also preferred and contemplated by the present invention.

[0022] Similarly, substituents for the aryl and heteroaryl groups are varied and are selected from: -halogen, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, -NO_2, -CO_2R', -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', -NR"$C(O)_2$R', ,-NR'-C(O)NR"R"', -$S(O)_2$R', -NH-$C(NH_2)$=NH, -NR'$C(NH_2)$=NH, -NH-$C(NH_2)$=NR', -S(O)R', -$S(O)_2$NR'R", -N_3, -$CH(Ph)_2$, perfluoro(C_1-C_4)alkoxy, and perfluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R" and R"' are independently selected from hydrogen, (C_1-C_8)alkyl and heteroalkyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-(C_1-C_4)alkyl, and (unsubstituted aryl)oxy-(C_1-C_4)alkyl.

[0023] Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -T-C(O)-$(CH_2)_q$-U-, wherein T and U are independently -NH-, -O-, -CH_2- or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -A-$(CH_2)_r$-B-, wherein A and B are independently -CH_2-, -O-, -NH-, -S-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NR'- or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula -$(CH_2)_s$-X-$(CH_2)_t$-, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, -$S(O)_2$-, or -$S(O)_2$NR'-. The substituent R' in -NR'- and -$S(O)_2$NR'- is selected from hydrogen or unsubstituted (C_1-C_6)alkyl.

[0024] As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

[0025] The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic

functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, ascorbic, propionic, isobutyric, maleic, malonic, lactic, malic, glutamic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, lactobionic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, 1977, **66**, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

[0026] The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

[0027] In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

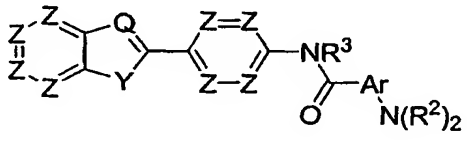
[0028] Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

[0029] Certain compounds of the present invention possess asymmetric carbon atoms (chiral centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present invention.

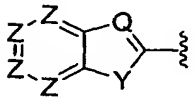
[0030] The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

Compounds

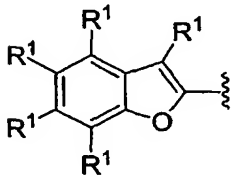
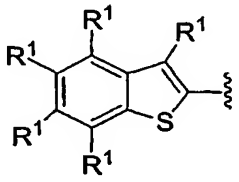
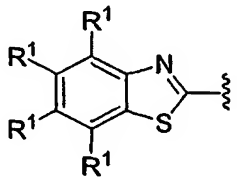
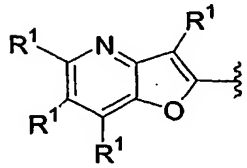
[0031] Preferred embodiments of compound (I) of this invention are now discussed.

[0032]  (1)

[0033] The 6,5-fused ring system in compound (I)



preferably is selected from the group consisting of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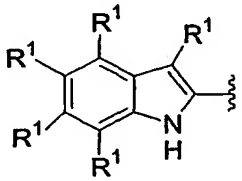
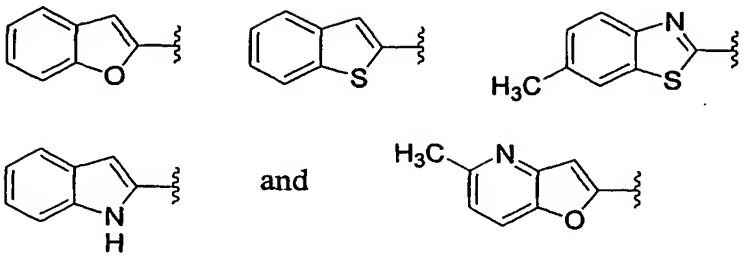
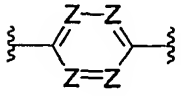


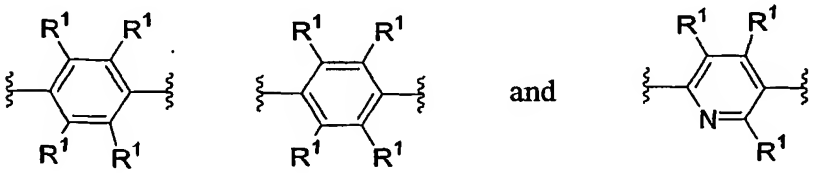
(where R^1 is as previously defined, with H and CH_3 being preferred R^1 groups); with the following 6,5-fused ring systems being particularly preferred:



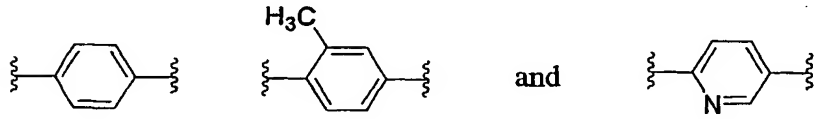
[0034] The 6-member ring



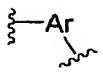
adjacent to the 6,5-fused ring system preferably is selected from the group consisting of



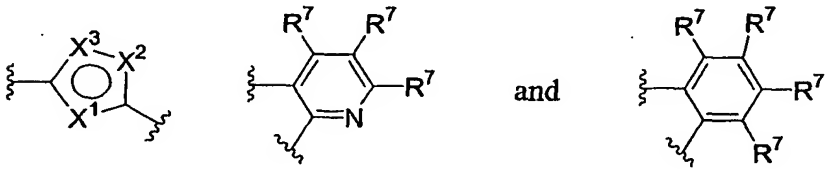
(where R^1 is as previously defined, with H and CH_3 being preferred R^1 groups); with the following 6-member rings being particularly preferred:



[0035] The divalent residue



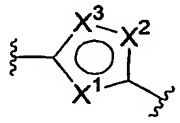
preferably is selected from the group consisting of



wherein one of X^1, X^2, and X^3 is a ring vertex selected from the group consisting of -O-, -S-, and $-NR^8$-, and the other two of X^1, X^2, and X^3 are ring vertices selected from the group consisting of =N- and $=CR^7$-; each R^7 is independently H, F, Cl, Br, I, CN, OH, NO_2, NH_2, a substituted or unsubstituted (C_1-C_{12})alkyl group, a substituted or unsubstituted (C_1-

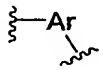
C_{12})alkoxy group, or a substituted or unsubstituted (C_1-C_{12})heteroalkyl group; and R^8 is H, a substituted or unsubstituted (C_1-C_{12})alkyl group, or a substituted or unsubstituted (C_1-C_{12})heteroalkyl group.

[0036] The residue



is a 5-membered ring heteroaromatic moiety, the selection of X^1, X^2, and X^3 determining the type of heteroaromatic ring. Exemplary heteroaromatic rings include imidazole, pyrrole, pyrazole, furan, isothiazole, oxazole, isoxazole, thiazole, furazan, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, 1,3,4-oxadiazole, 1,2,4-oxadiazole, and thiophene. The circle in the five-membered rings of formula is meant to indicate the presence of two double bonds, which, in some embodiments, can move within the ring.

[0037] Specific examples of moieties



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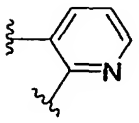
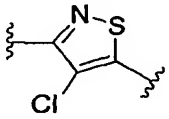
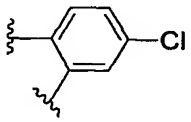
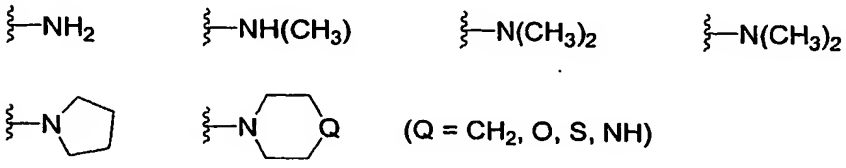
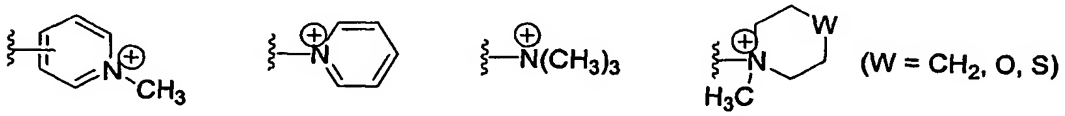


and


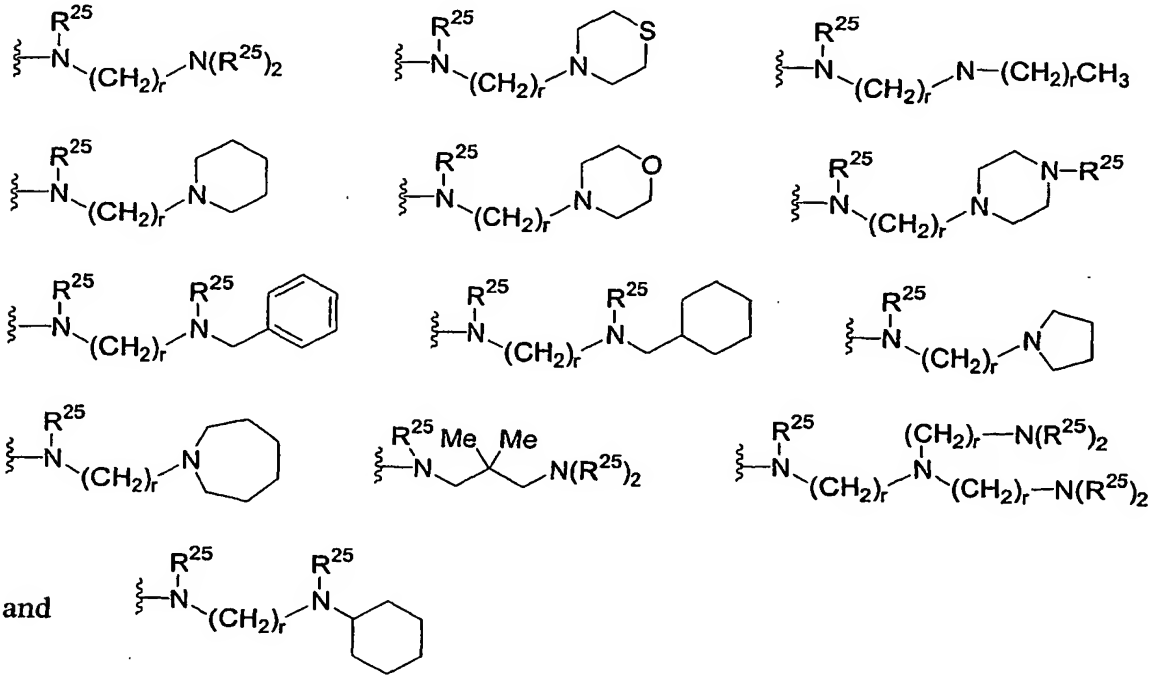
[0038] Compounds (I) have an alkyl amine group or a quaternary nitrogen group. Exemplary amine groups include



and the like. Exemplary quaternary nitrogen groups include

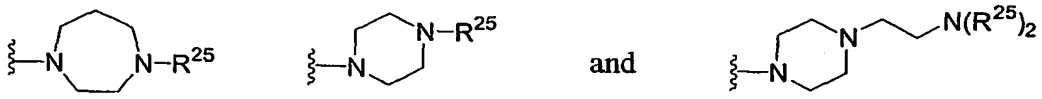


[0039] In a preferred embodiment, each R^2 is attached to the nitrogen atom via an sp^3 carbon, as illustrated by the following illustrative groups $N(R^2)_2$.



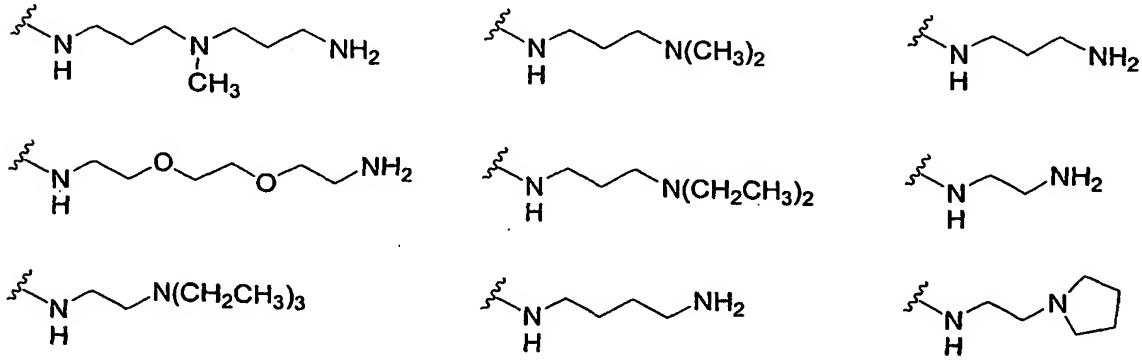
and

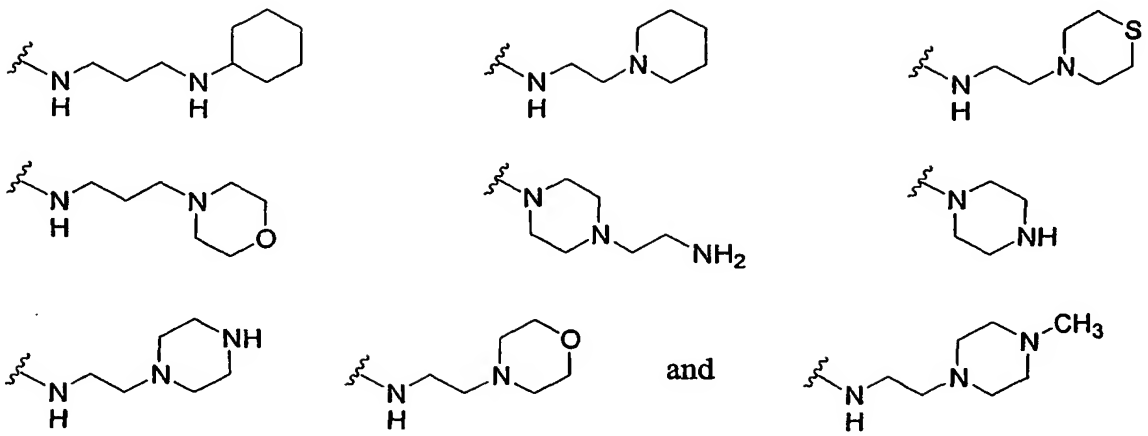
[0040] The two R^2's can join together with the nitrogen atom to which they are attached to form a 5, 6, or 7 member ring, as in



[0041] In the foregoing formulae, r is an integer ranging from 2 to 8, inclusive (preferably 2 to 6), and each R^{25} is independently H, CH_3, CH_2CH_3, $CH_2CH_2CH_3$, or $CH(CH_3)_2$.

[0042] Specific preferred $N(R^2)_2$ groups include:

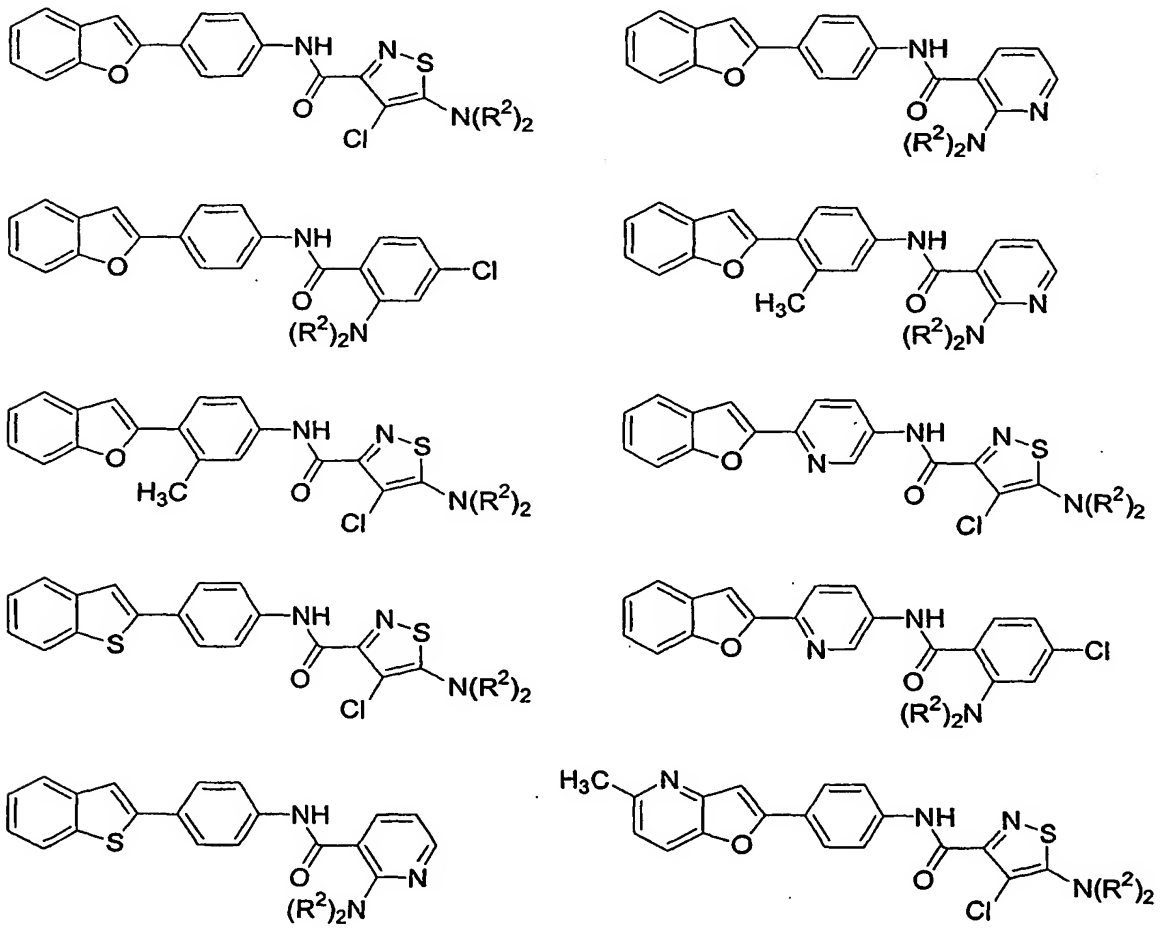


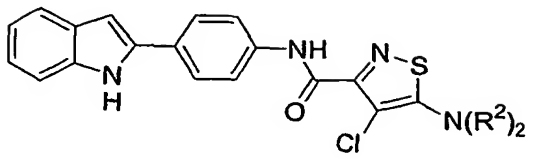
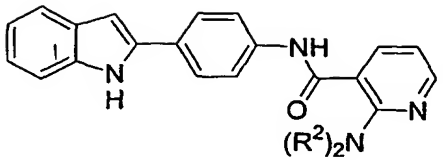
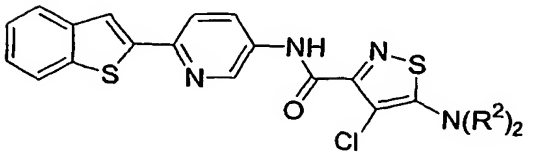
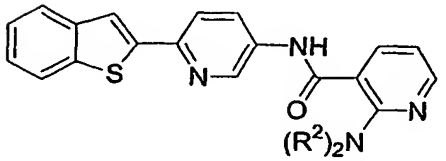
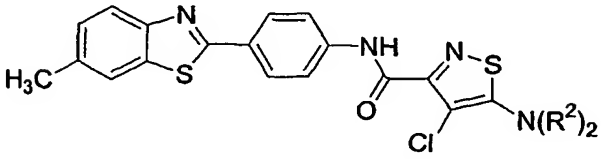


and

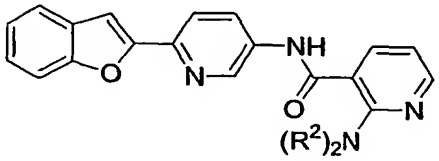
[0043] R^3 preferably is H, but it may be an alkyl group such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, and the like.

[0044] Preferred subgenera of compounds (I) are



and


;

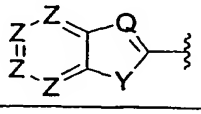
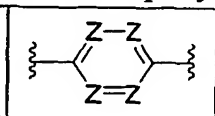
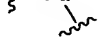
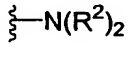
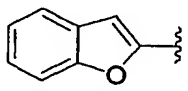
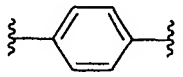
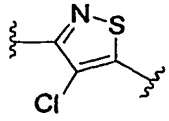
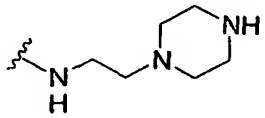
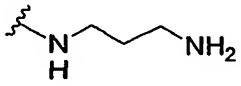
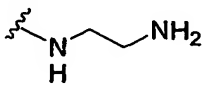
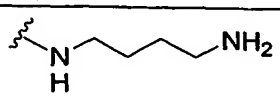
and the pharmaceutically acceptable salts thereof,

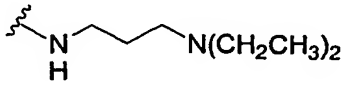
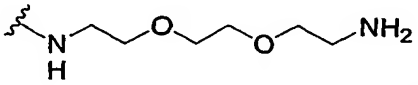
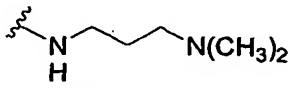
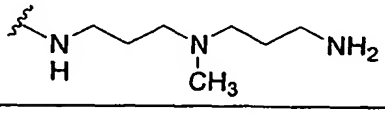
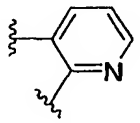
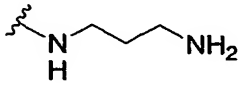
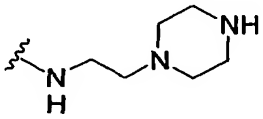
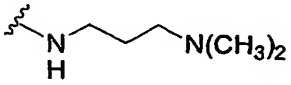
wherein each R^2 is independently H or a C_1 to C_{18} alkyl or heteroalkyl moiety or the two R^2's taken together with the nitrogen atom to which they are attached form a substituted or unsubstituted heteroalkyl 5 to 7 member ring; at least one group R^2 containing an alkyl amine group.

[0045] Examples of specific compounds (I) are shown in Table A.

[0046]

Table A — Exemplary Compounds of Formula (I)

Ref.				
A-1				
A-2	Same	Same	Same	
A-3	Same	Same	Same	
A-4	Same	Same	Same	

A-5	Same	Same	Same	
A-6	Same	Same	Same	
A-7	Same	Same	Same	
A-8	Same	Same	Same	
A-9	Same	Same		
A-10	Same	Same	Same	
A-11	Same	Same	Same	

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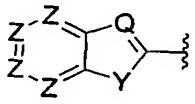
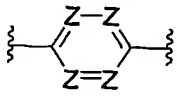
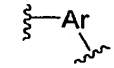
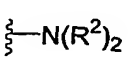
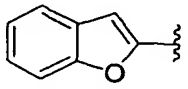
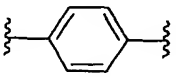
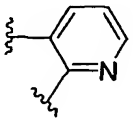
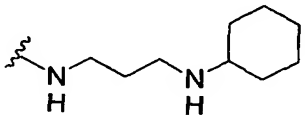
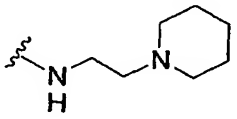
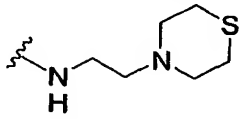
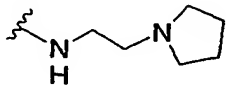
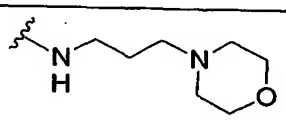
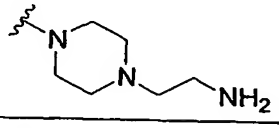
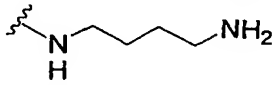
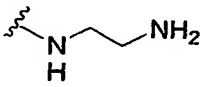
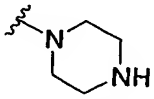
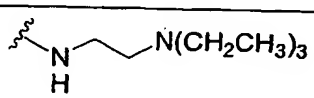
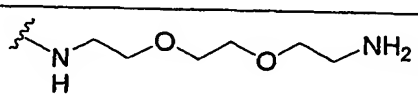
Ref.				
A-12				
A-13	Same	Same	Same	
A-14	Same	Same	Same	
A-15	Same	Same	Same	
A-16	Same	Same	Same	
A-17	Same	Same	Same	
A-18	Same	Same	Same	
A-19	Same	Same	Same	
A-20	Same	Same	Same	
A-21	Same	Same	Same	
A-22	Same	Same	Same	

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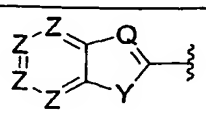
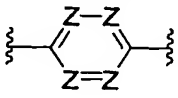
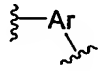
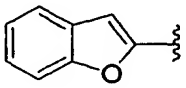
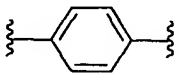
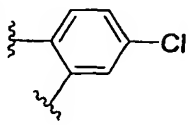
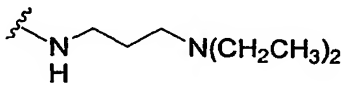
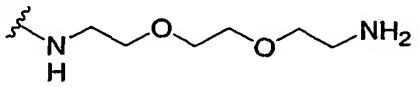
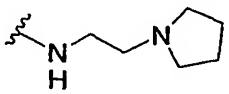
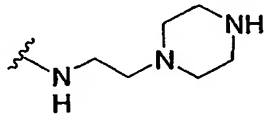
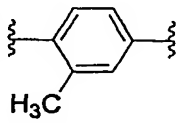
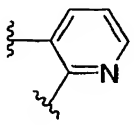
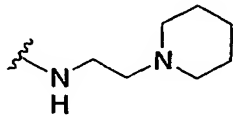
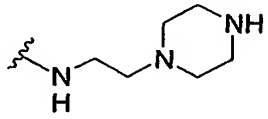
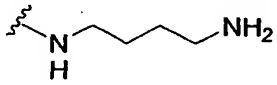
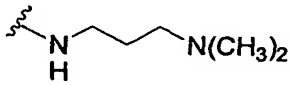
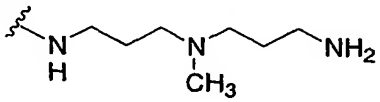
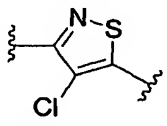
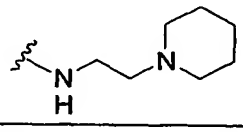
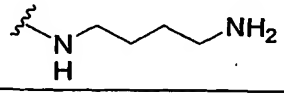
Ref.				
A-23				
A-24	Same	Same	Same	
A-25	Same	Same	Same	
A-26	Same	Same	Same	
A-27	Same			
A-28	Same	Same	Same	
A-29	Same	Same	Same	
A-30	Same	Same	Same	
A-31	Same	Same	Same	
A-32	Same	Same		
A-33	Same	Same	Same	

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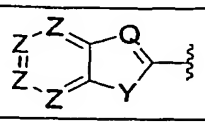
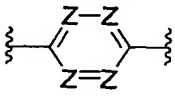
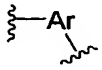
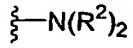
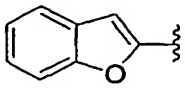
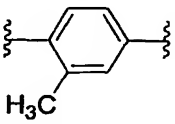
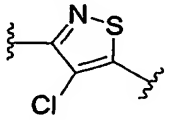
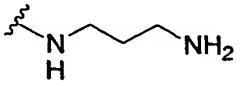
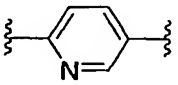
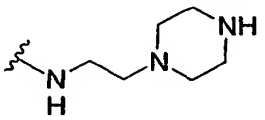
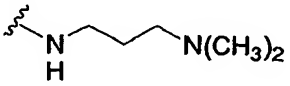
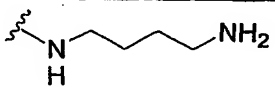
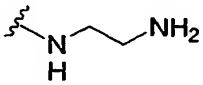
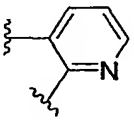
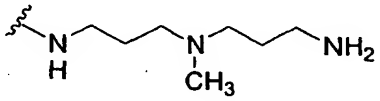
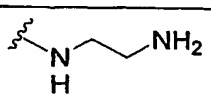
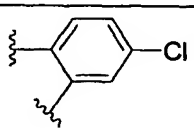
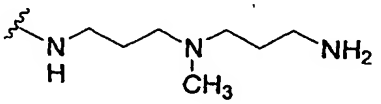
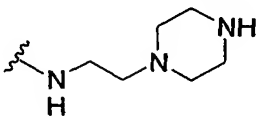
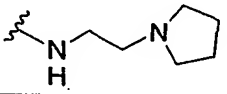
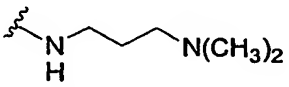
Ref.				
A-34				
A-35	Same		Same	
A-36	Same	Same	Same	
A-37	Same	Same	Same	
A-38	Same	Same	Same	
A-39	Same	Same		
A-40	Same	Same	Same	
A-41	Same	Same		
A-42	Same	Same	Same	
A-43	Same	Same	Same	
A-44	Same	Same	Same	

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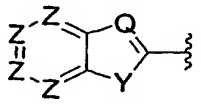
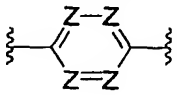
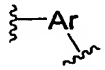
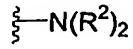
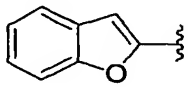
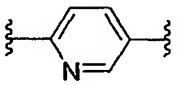
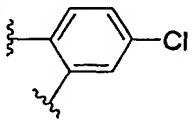
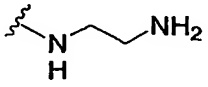
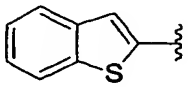
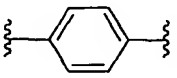
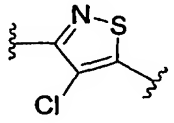
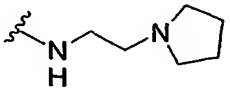
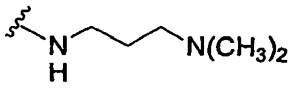
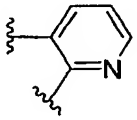
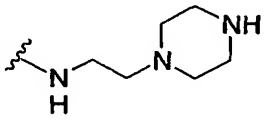
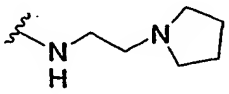
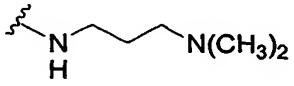
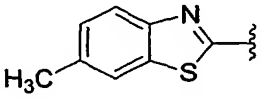
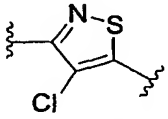
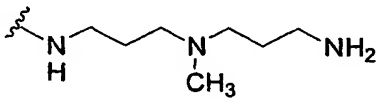
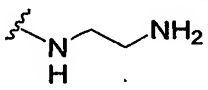
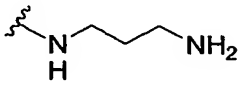
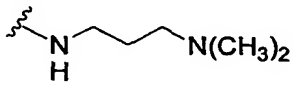
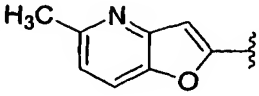
Ref.				
A-45				
A-46				
A-47	Same	Same	Same	
A-48	Same	Same		
A-49	Same	Same	Same	
A-50	Same	Same	Same	
A-51		Same		
A-52	Same	Same	Same	
A-53	Same	Same	Same	
A-54	Same	Same	Same	
A-55		Same	Same	Same

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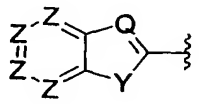
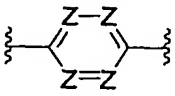
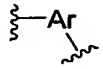
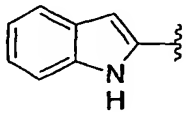
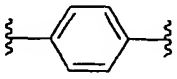
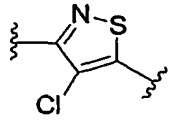
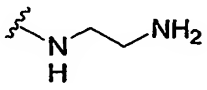
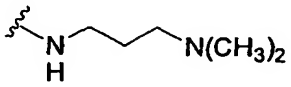
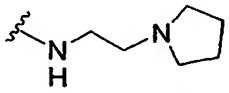
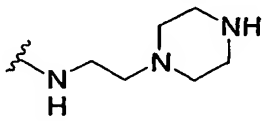
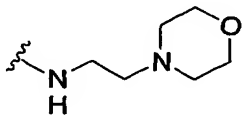
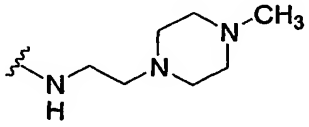
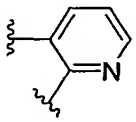
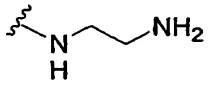
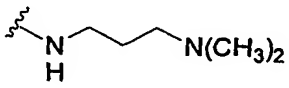
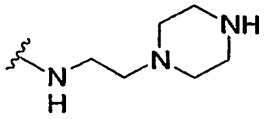
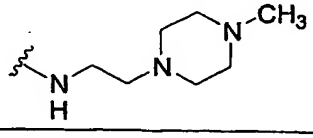
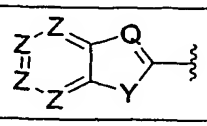
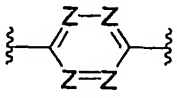
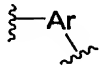
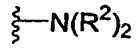
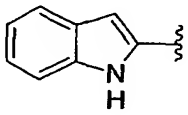
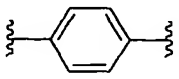
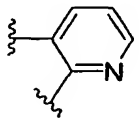
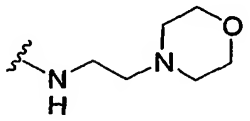
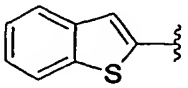
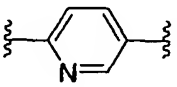
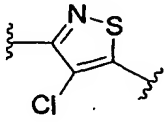
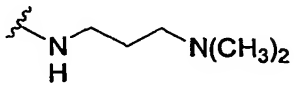
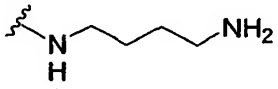
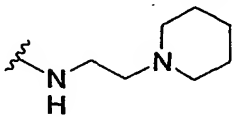
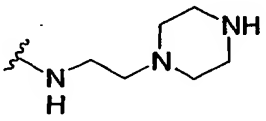
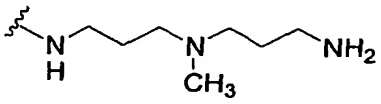
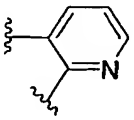
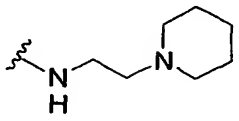
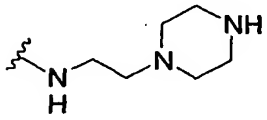
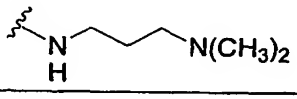
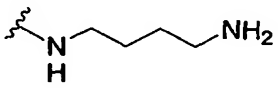
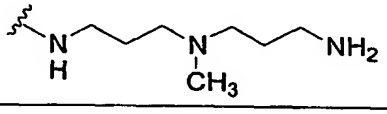
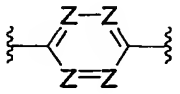
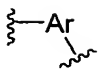
Ref.				
A-56				
A-57	Same	Same	Same	
A-58	Same	Same	Same	
A-59	Same	Same	Same	
A-60	Same	Same	Same	
A-61	Same	Same	Same	
A-62	Same	Same		
A-63	Same	Same	Same	
A-64	Same	Same	Same	
A-65	Same	Same	Same	

Table A (continued)				
Ref.				
A-66				
A-67				
A-68	Same	Same	Same	
A-69	Same	Same	Same	
A-70	Same	Same	Same	
A-71	Same	Same	Same	
A-72	Same	Same		
A-73	Same	Same	Same	
A-74	Same	Same	Same	
A-75	Same	Same	Same	
A-76	Same	Same	Same	

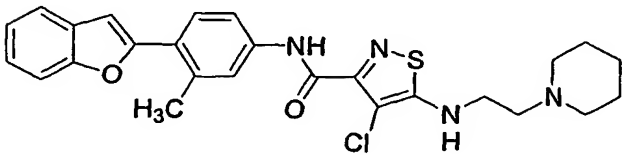
[0047] In the entries in Table A, where a divalent residue



or

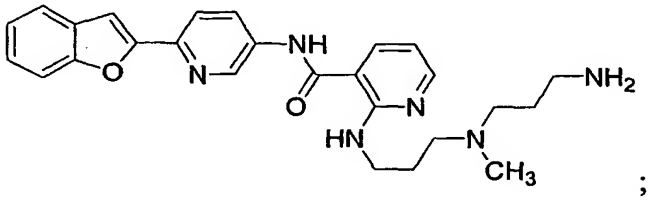


is asymmetric, it is to be inserted into formula (I) in the orientation depicted to arrive at the specific compound at issue. (This statement is not to be construed as meaning that such an asymmetric residue only can be used in compounds of this invention in the depicted orientation; in the context of a different compound, it can be used in the reversed orientation.) By way of illustration, the fully written out structure of compound A-32 is



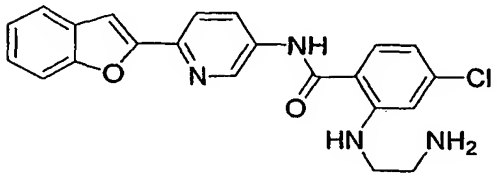
;

while the fully written out structure of compound A-39 is



;

and the fully written out structure of compound A-45 is



and so forth.

[0048] Compounds of this invention have been found to have anti-bacterial and/or antifungal properties and therefore may be used for combating (i.e., preventing and/or treating) infections in eukaryotic organisms. For human anti-infective applications, an effective amount of a compound of this invention is used, optionally in combination with a pharmaceutically acceptable carrier. The composition may be dry, or it may be a solution. Treatment may be reactive, for combating an existing infection, or prophylactic, for preventing infection in an organism susceptible to infection. Preferably, compounds of this invention are used to treat infections by drug-resistant strains of bacteria, for example MRSA

(methicillin resistant *S. aureus*), MRSE (methicillin resistant *S. epidermidis),* PRSP (penicillin resistant *S. pneumoniae*) or VRE (vancomycin resistant *Enterococci*). By "drug-resistant" it is meant that the bacteria are resistant to treatment with conventional antibiotics.

[0049] Host organisms that can be treated include eukaryotic organisms, in particular plants and animals. The plant may be an agriculturally important crop, such as wheat, rice, corn, soybean, sorghum, and alfalfa. Animals of interest include mammals such as bovines, canines, equines, felines, ovines, porcines, and primates (including humans). Thusly, in another aspect of this invention, there is provided a method for treating a bacterial infection — particularly an infection by Gram-positive bacteria — comprising administering to a patient in need of such treatment an effective amount of compound (I). Compounds of this invention can be used in the preparation of a medicament for treating a bacterial infection in a mammal. The compounds may be administered orally, topically, parenterally (e.g., intravenously, subcutaneously, intraperitoneally, transdermally) or by inhalation.

Synthesis — General Remarks

[0050] Typically, the structures of compounds were confirmed by ^{1}H-NMR and/or mass spectrometry. Where a parenthetical remark such as "^{1}H-NMR" or "mass spectrum" or "ESI-MS" follows a reference to a compound without any elaboration, it means that such spectrum was taken, was consistent with the assigned structure, and did not indicate the presence of significant impurities.

[0051] Abbreviations in common usage are employed for various technical terms, solvents, catalysts and reagents, including: HBTU for 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyl-uronium hexafluorophosphate; DIEA for diisopropylethylamine; DMF for N,N-dimethyl-formamide; TFA for trifluoroacetic acid; NMP for N-methylpyrrolidone; Boc for t-butyl-oxycarbonyl; RT for room temperature; and TLC for thin layer chromatography.

[0052] The skilled artisan will understand: (a) that an intermediate described in the context of the synthesis of a particular compound of this invention can also be used to make other compounds of this invention, *mutatis mutandis*; (b) that in certain experimental sections only the preparation of an intermediate compound is described, because its incorporation into a final compound of this invention straightforwardly follows synthetic methodology described herein; and (c) that, for some reactions that recur herein, detailed reaction and work-up conditions sometimes are not provided in each instance in the interest of brevity and that the

conditions described elsewhere in this application are adaptable to the instance at hand without undue experimentation.

Synthesis — General Procedures

[0053] The following recurring general procedures are cited as "Procedure A," "Procedure B," etc. in the subsequent experimental sections.

[0054] Procedure A: Suzuki-type coupling of a boronic acid and an aryl halide. A degassed suspension of the boronic acid (1.1 equiv.), $PdCl_2(PPh_3)_2$ (0.05 equiv.), and Na_2CO_3 (5 equiv.) in DMF/H_2O (2:1) was treated at RT under N_2 with a degassed (N_2) solution of the aryl halide (1.0 equiv.) in DMF ($^1/_4$ of total volume). The mixture was heated to 80°C for 3hr (the reaction was followed by TLC and worked up after complete consumption of the starting material), cooled to RT, diluted with AcOEt, and washed with H_2O (2x). The organic layer was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography to give the product as a solid.

[0055] *Procedure B: Deprotection of a Boc-Protected Amine.* A mixture of the Boc-protected amine (1 equiv.) in TFA was stirred at RT for 1 hr, treated with MeOH ($^1/_2$ of reaction volume), and left for 15 min. Evaporation of the solvent gave the deprotected amine product, used without further purification.

[0056] *Procedure C: Coupling of an acid chloride to an aryl amine.* A mixture of the acid chloride (1.2 equiv.) and the amine (1.0 equiv.) in DMF/DIEA (ca. 3:1) was stirred at 60°C for 12-18 hr. The mixture was added dropwise to ice-water containing ca. 10% K_2CO_3 (ca. 40 fold the reaction volume). The resulting precipitate was collected by filtration and dried.

[0057] *Procedure D: Nucleophilic aromatic substitution.* A mixture of a dichloroisothiazole, a 2-chloronicotinamide, or a 4-chloro-2-fluorobenzamide (1 equiv.) in a solution of an amine in NMP (2:1) was stirred at 60-75°C for 24 to 72 hr and diluted with 50% aqueous AcOH to a final volume of 15 mL (where noted below, DIEA was added to the reaction mixture). The crude product was purified by RP-HPLC (Hamilton PRP-1 column, CH_3CN/0.5% aq AcOH, 0% to 60% in 60 min). The purified product was characterized by ^{1}H-NMR and ESI-MS).

Synthesis — Compounds

Example A

[0058] This example describes the synthesis of compounds (I) containing a benzofuryl-phenylene moiety.

[0059] Reference is made to Fig. 1, which shows the preparation of intermediates **11** to **13**. Instead of acid chlorides **6**, **8**, and **10**, the corresponding acids can be used to prepare intermediates **11**, **12**, and **13** (using HBTU-mediated coupling).

[0060] *Compound 3*. A mixture of 4-iodoaniline **2** (9.39 g, 42.8 mmol) and Boc_2O (8.78 g, 47.1 mmol) in DMF (25 mL) and DIEA (5 mL) was stirred at RT for 3 hr, diluted with AcOEt (300 mL), and washed with H_2O (2x, each 150 mL). The organic layer was dried ($MgSO_4$) and evaporated to give compound **3** (11.89 g, 87%, ^{1}H-NMR).

[0061] *Compound 4*. Coupling of compounds **1** (679 mg, 4.19 mmol) and **3** (1.21 g, 3.79 mmol) according to procedure A gave compound **4** (0.50 g, 43%, white powder, ^{1}H-NMR).

[0062] *Compound 5*. A solution of compound **4** (472 mg) in AcOEt (150 mL, saturated with anhydrous HCl gas) was stirred at RT for 4 hr and diluted with Et_2O (100 mL). The resulting precipitate was collected by filtration and dried to give compound **5** (315 mg, >95%, ^{1}H-NMR).

[0063] *Compound 11*. A mixture of acid **7** (1.06 g, 5.35 mmol) and HBTU (1.93 g, 5.09 mmol) in NMP (4 mL) and DIEA (1 mL) was stirred at RT for 40 min and added to a solution of compound **5** (0.935 g, 4.47 mmol) in NMP (2 mL) and DIEA (0.5 mL). The mixture was stirred for 1 hr at RT and added dropwise to 10% aqueous K_2CO_3 (200 mL) at ca. 4°C. The resulting precipitate was collected by filtration and dried *in vacuo* to give compound **11** (^{1}H-NMR; used without further purification).

[0064] *Compound 12*. A mixture of acid **9** (1.04 g, 6.62 mmol) and HBTU (2.39 g, 6.30 mmol) in NMP (9 mL) and DIEA (1.5 mL) was stirred at 37°C for 30 min and added to a solution of compound **5** (1.16 g, 5.55 mmol) in NMP (2 mL) and DIEA (0.5 mL). The mixture was stirred for 17 hr at RT followed by 5 hr at 60°C and added dropwise to 10% aqueous K_2CO_3 (400 mL) at ca. 4°C. The resulting precipitate was collected by filtration and dried *in vacuo* to give compound **12** (1.70 g; ^{1}H-NMR spectrum; contained impurities but was used without further purification).

[0065] *Compound 13.* Coupling of acid chloride **10** (0.222 mL, 1.68 mmol) and compound **5** (0.318 g, 1.29 mmol) according to Procedure C gave compound **13** as a tan solid (505 mg, ^{1}H-NMR; contained minor impurities but was used without further purification).

[0066] Next, Fig. 2 illustrates the synthesis of compounds **A-1** to **A-26** from intermediates previously synthesized. The regioselectivity of the nucleophilic aromatic substitution at the isothiazole unit in intermediate **11** was confirmed by the X-ray structure of a model compound, while the structures of compounds **A-23** to **A-26** were unambiguously assigned by ^{1}H-NMR.

[0067] *Compounds A-1 to A-8.* These compounds were prepared from compound **11** (70 mg) in a mixture of the corresponding amine (0.3-1 mL) and NMP (0.1-0.5 mL), 60°C, 24 hours, according to Procedure D.

[0068] *Compounds A-9 to A-22.* Compounds **A-11** and **A-13** to **A-21** were prepared from compound **12** (80 mg) and the corresponding amine (ca. 0.2 mL) in NMP (1 mL) and DIEA (0.2 mL), 60°C, 17-24 hr, according to Procedure D. Compounds **A-9**, **A-10**, **A-12**, and **A-22** were prepared analogously.

[0069] *Compounds A-23 to A-26.* These compounds were prepared from compound **13** (50 mg) in a mixture of the corresponding amine (0.4 mL) and NMP (0.4 mL), 75°C, 24 hr, according to Procedure D.

Example B

[0070] This example describes the synthesis of biaryl compounds wherein the biaryl moiety comprises a benzofuryl unit and a methylated phenyl unit.

[0071] The synthesis of the intermediates **18** and **19** is shown in Fig. 3.

[0072] *Compound 15.* Compound **15** was prepared by Boc-protection of aniline **14** by analogy to the preparation of compound **3**.

[0073] *Compound 16.* Coupling of compounds **1** (1.55 g, 9.60 mmol) and **15** (2.50 g, 8.73 mmol) according to Procedure A gave intermediate **16** (2.00 g, 71%, white solid, ^{1}H-NMR).

[0074] *Compound 17.* Deprotection of intermediate **16** (2.00 g) according to Procedure B gave compound **17** (>95%, white solid, ^{1}H-NMR).

[0075] *Compound 18.* Coupling of compounds **17** (0.70 g, 2.07 mmol) and **6** (0.494 g, 2.28 mmol) according to Procedure C gave compound **18** (^{1}H-NMR).

[0076] *Compound 19.* Coupling of compounds **17** (0.70 g, 2.07 mmol) and **8** (0.40 g, 2.28 mmol) according to Procedure C gave compound **19** (^{1}H-NMR).

[0077] Intermediates **18** and **19** were converted to compounds **A-27** to **A-34**, as shown in Fig. 4.

[0078] *Compounds A-27 to A-31.* These compounds were prepared from compound **19** (80 mg) in a mixture of the corresponding amine H_2NR^2 (0.4 mL) and NMP (1 mL), 70°C, 72 hr, according to Procedure D.

[0079] *Compounds A-32 to A-34.* These compounds were prepared from compound **18** (80 mg) in a mixture of the corresponding amine H_2NR^2 (0.4 mL) and NMP (1 mL), 70°C, 72 hr, according to Procedure D.

Example C

[0080] This example describes the synthesis of compounds containing a benzofuryl moiety and various N-termini. The internal heterocyclic unit is a disubstituted pyridine. Intermediates **24** to **26** were prepared by Suzuki-type coupling of benzofuryl boronic acid **1** and chloropyridine **21** as the key step, as shown in Fig. 5.

[0081] *Compound 21.* A mixture of pyridine **20** (5.37 g, 41.9 mmol) and Boc_2O (8.56 g, 46.1 mmol) in DMF (25 mL) and DIEA (5 mL) was stirred at RT for 4 hr, then at 60°C for 16 hr. The solution was diluted with AcOEt (300 mL) and was washed with 10% aqueous K_2CO_3 (2x, each 100 mL). The organic layer was dried ($MgSO_4$) and evaporated to give compound **21** (8.27 g, 87%, ^{1}H-NMR).

[0082] *Compound 22.* Coupling of boronic acid **1** (841 mg, 5.19 mmol) and compound **21** (1.08 g, 4.72 mmol) according to Procedure A gave compound **22** (1.07 g, 73%, white crystals, ^{1}H-NMR).

[0083] *Compound 23.* A mixture of compound **22** (0.98 g) in AcOEt (50 mL, saturated with anhydrous HCl gas) was stirred at 0°C to RT for 9 hr and treated with Et_2O (200 mL). The resulting solid was collected by filtration and dried to give compound **23** as yellow crystals (0.759 g, 85%, ^{1}H-NMR).

[0084] *Compound 24.* Coupling of acid chloride **6** (1.34 g, 6.17 mmol) and compound **23** (2.00 g, 6.17 mmol) according to Procedure C gave compound **24** (^{1}H-NMR).

[0085] *Compound 25.* Coupling of acid chloride **8** (1.09 g, 6.17 mmol) and compound **23** (2.00 g, 6.17 mmol) according to Procedure C gave compound **25** (^{1}H-NMR; minor impurities but used for the next step without further purification).

[0086] *Compound 26.* Coupling of acid chloride **10** (0.815 mL, 6.17 mmol) and compound **23** (2.00 g, 6.17 mmol) according to Procedure C gave compound **26** (^{1}H-NMR; minor impurities but used for the next step without further purification).

[0087] The conversion of intermediates **24, 25,** and **26** to compounds **A-35** to **A-45** is shown in Fig. 6.

[0088] *Compounds A-35 to A-38.* These compounds were prepared from compound **24** (80 mg) in a mixture of the corresponding amine H_2NR^2 (0.4 mL) and NMP (1 mL), 75°C, 48 hr, according to Procedure D.

[0089] *Compounds A-39 and A-40.* These compounds were prepared from compound **25** (100 mg for compound **A-39**; 80 mg for compound **A-40**) in a mixture of the corresponding amine H_2NR^2 (0.5 mL for compound **A-39**; 0.4 mL for compound **A-40**) and NMP (0.5 mL for compound **A-39**; 1 mL for compound **A-40**), 75°C, 48 hr, according to Procedure D.

[0090] *Compounds A-41 to A-45.* These compounds were prepared from compound **26** (80 mg; except 100 mg for compound **A-41**) in a mixture of the corresponding amine H_2NR^2 (0.4 mL; except 0.5 mL for compound **A-41**) and NMP (1 mL; except 0.5 mL for **A-41**), 75°C, 48 hr, according to Procedure D.

Example D

[0091] This example describes the synthesis of compounds having a ring nitrogen in the benzofuryl unit, as exemplified by compound **A-55**.

[0092] The key step is a Sonogashira-type coupling of arylalkyne **29** to iodopicolinol **27** (Fig. 7). The product of the C-C bond formation spontaneously undergoes a Pd-mediated cyclization to desired product **30**. Deprotection of product **30** under acidic conditions gave aniline **31**, which was coupled to acid chloride **6** to yield intermediate **32**. Nucleophilic aromatic substitution at the isothiazole ring in intermediate **32** gave compound **A-55**.

[0093] *Compound 29*. Compound **29** was prepared by Boc-protection of compound **28**, analogously to the preparation of compound **3**.

[0094] *Compound 30*. A degassed (N_2) suspension of picolinol **27** (0.50 g, 2.12 mmol), $PdCl_2(PPh_3)_2$ (30 mg, 0.04 mmol), CuI (32 mg, 0.17 mmol), and PPh_3 (44 mg, 0.16 mmol) in Et_3N (10 mL) was treated at RT with alkyne **28** (508 mg, 2.34 mmol) and stirred at 70°C for 2 hr. Evaporation of the solvent and purification of the residual material by flash chromatography (hexane/AcOEt, 19:1 to 3:2 gradient) gave compound **30** (153 mg, 22%, ^{1}H-NMR).

[0095] *Compound 31*. Compound **30** (100 mg) in AcOEt (4 mL, saturated with anhydrous HCl gas) was stirred at RT for 6 hr and diluted with Et_2O (50 mL). The resulting precipitate was collected by filtration and dried to give compound **31** as a yellow solid (85 mg, 93%, ^{1}H-NMR).

[0096] *Compound A-55*. A mixture of acid chloride **6** (17.2 mg, 80 μmol) and amine **31** (20 mg, 67 μmol) in NMP (0.33 mL) and DIEA (0.03 mL) was stirred at 60°C for 12 hr to give compound **32**, which was converted *in situ* to compound **A-55** by treatment with 3-(dimethylamino)propylamine (1 mL), stirring at 70°C for 24 hr, dilution with 50% aqueous AcOH to a total volume of 15 mL and purification by HPLC (^{1}H-NMR, ESI-MS).

Example E

[0097] This example describes the synthesis of compounds containing a benzothienyl moiety. As shown in Fig. 8, the benzothienyl-containing biaryl unit was formed under Suzuki-type conditions starting from boronic acid **33** and iodoaniline **3**.

[0098] *Compound 34*. Coupling of boronic acid **33** (1.50 g, 8.42 mmol) and protected iodoaniline **3** (2.44 g, 7.66 mmol) according to Procedure A gave biaryl compound **34** (1.56 g, 63%, tan solid, ^{1}H-NMR).

[0099] *Compound 35*. Deprotection of biaryl compound **34** (1.56 g) according to Procedure B gave **35** (>95%, ^{1}H-NMR; contained residual TFA but used without further purification).

[0100] *Compound 36*. Coupling of acid halide **6** (498 mg, 2.30 mmol) and compound **35** (650 mg, 1.92 mmol) according to Procedure C gave triaryl compound **36** (^{1}H-NMR).

[0101] *Compound 37*. Coupling of acid halide **8** (405 mg, 2.30 mmol) and compound **35** (650 mg, 1.92 mmol) according to Procedure C gave triaryl compound **37** (^{1}H-NMR).

[0102] The preparation of compounds **A-46** to **A-50** from triaryl intermediates **36** and **37** is illustrated in Fig. 9.

[0103] *Compounds A-46 and A-47.* These compounds were prepared from compound **36** (80 mg) in a mixture of the corresponding amine H_2NR^2 (0.4 mL) and NMP (1 mL), 75°C, 48 hr, according to Procedure D.

[0104] *Compounds A-48 to A-50.* These compounds were prepared from compound **37** (80 mg) in a mixture of the corresponding amine H_2NR^2 (0.4 mL) and NMP (1 mL), 75°C, 48 hr, according to Procedure D.

Example F

[0105] This example describes the synthesis of compounds containing a benzothiazole moiety from the commercially available compound **38** (Fig. 10).

[0106] *Compound 39.* A mixture of acid **7** (1.812 g, 9.20 mmol) and HBTU (3.314 g, 8.74 mmol) in DMF (10 mL) and DIEA (3 mL) was stirred at RT for 1 hr. The mixture was added to a solution of compound **38** (2.0 g, 8.32 mmol) in DMF (16 mL) and DIEA (2 mL). The reaction mixture was stirred at 60°C for 24 hr and poured into stirred ice-water (ca. 700 mL). The resulting precipitate was collected by filtration and dried to give compound **39** as a tan solid (2.33 g) (^{1}H-NMR; minor impurities but used without further purification).

[0107] *Compounds A-51 to A-54.* These compounds were prepared according to Procedure D using compound **39** (100 mg), the corresponding amine H_2NR^2 (0.4 mL), NMP (1 mL), and DIEA (0.1 mL).

Example G

[0108] This example describes the synthesis of compounds in which the biaryl unit contains an indole moiety.

[0109] Fig. 11 shows the synthesis of intermediates **43** and **44**.

[0110] *Compound 41.* Coupling of protected boronic acid **40** (1.00 g, 3.83 mmol) and protected iodoaniline **3** (1.11 g, 3.48 mmol) according to Procedure A gave compound **41** (1.19 g, 83%, tan solid, ^{1}H-NMR).

[0111] *Compound 42.* Deprotection of compound **41** (1.19 g) according to Procedure B gave compound **42** (923 mg; >95%; ^{1}H-NMR; contained residual TFA but used without further purification).

[0112] *Compound 43.* Coupling of acid halide **6** (378 mg, 1.75 mmol) and compound **42** (450 mg, 1.40 mmol) according to Procedure C gave intermediate **43** (^{1}H-NMR).

[0113] *Compound 44.* Coupling of acid halide **8** (321 mg, 1.82 mmol) and compound **42** (470 mg, 1.46 mmol) according to Procedure C gave compound **44** (^{1}H-NMR; minor impurities but used without further purification).

[0114] Fig. 12 shows the conversion of compounds **43** and **44** to compounds of this invention.

[0115] *Compounds A-56 and A-61.* These compounds were prepared from compound **43** (70 mg) in a mixture of the corresponding amine H_2NR^2 (0.4 mL) and NMP (1 mL), 75°C, 48 hr, according to Procedure D.

[0116] *Compounds A-62 and A-66.* These compounds were prepared from compound **44** (80 mg) in a mixture of the corresponding amine H_2NR^2 (0.4 mL) and NMP (1 mL), 75°C, 48 hr, according to Procedure D.

Example H

[0117] This example describes the synthesis of compounds in which the biaryl moiety is a benzothienyl-pyridyl moiety.

[0118] Fig. 13 shows the synthesis of intermediates **48** and **49**.

[0119] *Compound 46.* Coupling of boronic acid **45** (2.00 g, 11.2 mmol) and chloropyridine **21** (2.34 g, 10.2 mmol) according to Procedure A gave biaryl compound **46** (1.94 g, 58%, white solid, ^{1}H-NMR).

[0120] *Compound 47.* Deprotection of biaryl compound **46** (2.40 g) according to Procedure B gave compound **47** (2.40 g, orange solid, ^{1}H-NMR, contained residual TFA but used without further purification).

[0121] *Compound 48.* Coupling of acid chloride **6** (525 mg, 2.42 mmol) and compound **47** (750 mg, 2.20 mmol) according to Procedure C gave intermediate **48** (used without characterization).

[0122] *Compound 49*. Coupling of acid chloride **8** (427 mg, 2.42 mmol) and compound **47** (750 mg, 2.20 mmol) according to Procedure C gave intermediate **49** (used without characterization).

[0123] Fig. 14 shows the conversion of intermediates **48** and **49** to compounds of this invention.

[0124] *Compounds A-67 to A-71*. These compounds were prepared from intermediate **48** (100 mg) in a mixture of the corresponding amine H_2NR^2 (0.5 mL) and NMP (0.5 mL), 75°C, 48 hr, according to Procedure D.

[0125] *Compounds A-72 to A-76*. These compounds were prepared from intermediate **49** (100 mg) in a mixture of the corresponding amine H_2NR^2 (0.5 mL) and NMP (0.5 mL), 75°C, 48 hr, according to Procedure D.

Biological Activity

[0126] *In vitro* biological activity data were collected for a variety of microorganisms, including *Bacillus cereus* (ATCC 11778), *Staphylococcus aureus* (ATCC 33591; ATCC 27660, a methicillin resistant strain (MRSA); ATCC 13709, a methicillin sensitive strain (MSSA)), *Escherichia coli* (ATCC 25922), *Enterococcus faecalis* (ATCC 29212), *Streptococcus pneumoniae* (ATCC 49619; ATCC 51422, a penicillin resistant strain (PRSP)), *Enterococcus faecium* (ATCC 51559, a vancomycin resistant strain (VRE)), and *Staphylococcus epidermidis* (ATCC 12228). Additionally, antifungal activity data were collected for *Candida albicans* (ATCC 38247). Compounds of this invention preferably have an MIC of 4 or less against a drug resistant bacterial strain, such as one of the foregoing (MRSA, VRE, PRSP)

[0127] Compounds according to this invention were screened for their *in vitro* activities against selected species of bacteria and fungi. The minimal inhibition concentration (MIC) of these compounds was determined using the National Committee for Clinical Laboratory Standards (NCCLS) broth microdilution assay in microtiter plates, as set forth in: (1) the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS) Document M7-A4 (NCCLS, 1997); (2) the guidelines of the National Committee for Clinical Laboratory Standards (NCCLS) Document M11-A4 (NCCLS, 1997); and (3) the guidelines and reference method of the National Committee for Clinical Laboratory Standards (NCCLS) Document M27-

T (NCCLS, 1995). For antifungal assays, the method recommended in Murray, PR., *1995 Manual of Clinical Microbiology* (ASM Press, Washington, DC.), was employed.

[0128] Preferably, compounds of this invention have an MIC of 4 or less against at least one strain of drug resistant bacteria. The results are presented in Table B below, which is keyed as follows:

Key to organisms tested against:

A = *B. cereus* ATCC 11778	B = *C. albicans* ATCC 38247
C = *E. faecalis* ATCC 29212	D = *S. aureus* ATCC 13709
E = *S. aureus* ATCC 27660	F = *S. aureus* ATCC 33591
G = *S. epidermidis* ATCC 12228	H = *S. pneumoniae* ATCC 49619
I = *E. coli* ATCC 25922	

Key to activity:

+++ = MIC ≤ 4	++ = $4 <$ MIC < 12
+ = $12 \leq$ MIC ≤ 32	ND = not determined
>32 = preliminary data indicates MIC greater than 32	

Table B — Biological Activity									
	Organism (Minimum Inhibitory Concentration (MIC), μg/mL)								
Ref.	A	B	C	D	E	F	G	H	I
A-1	+++	+	+++	+++	+++	ND	ND	+	>32
A-2	+++	++	+++	+++	+++	+++	+++	+	>32
A-3	+	+++	+++	+++	+++	+++	+++	+	>32
A-4	+	+	+++	+++	+++	ND	ND	>32	>32
A-5	++	++	+++	+++	+++	ND	ND	>32	>32
A-6	>32	++	+++	+++	+++	ND	ND	>32	>32
A-7	+++	++	+++	+++	+++	+++	+++	+	>32
A-8	+++	++	+++	+++	+++	+++	+++	+	+
A-9	+++	+	+++	+++	+++	ND	ND	+	+
A-10	+	>32	+	ND	ND	ND	ND	+	>32
A-11	+++	+++	+++	+++	+++	+++	+++	+	>32
A-12	+	+	++	ND	ND	ND	+	++	>32
A-13	+++	+	+++	+++	+++	ND	ND	+	>32
A-14	>32	>32	>32	>32	>32	ND	ND	>32	>32
A-15	++	+	+++	+++	+++	ND	ND	+	>32
A-16	>32	+	++	+++	+++	ND	ND	+	>32
A-17	+	+	+	++	+	ND	ND	+	>32
A-18	+++	++	++	+++	+++	+++	+++	+++	>32
A-19	+++	++	+++	+++	+++	+++	+++	+	>32
A-20	+	++	+	++	++	ND	ND	+	+
A-21	++	+++	+++	+++	+++	ND	ND	+	>32
A-22	++	+++	++	++	++	ND	ND	+	>32
A-23	+++	+	+++	+++	+++	+++	ND	+	>32
A-24	>32	>32	+	+	+	+	ND	>32	>32
A-25	>32	>32	+	+	+	+	ND	>32	>32

Table B (continued)

Ref.	Organism (Minimum Inhibitory Concentration (MIC), μg/mL)								
	A	B	C	D	E	F	G	H	I
A-26	+	>32	++	+++	++	++	ND	+	>32
A-27	++	++	+++	+++	+++	+++	ND	+	>32
A-28	+	+	++	++	++	++	ND	+	>32
A-29	+++	+	+++	+++	+++	+++	ND	+	>32
A-30	++	+	+++	+++	+++	+++	ND	+	>32
A-31	++	++	+++	+++	+++	+++	ND	+	++
A-32	>32	++	+++	+++	+++	+++	+++	ND	+
A-33	>32	+	++	+++	+++	+	ND	+	>32
A-34	+++	+++	+++	+++	+++	+++	+++	+	>32
A-35	>32	+++	+	+	+	>32	ND	>32	>32
A-36	++	++	++	+++	+	++	ND	+	>32
A-37	>32	+	++	+++	+++	++	ND	>32	>32
A-38	+++	+	+++	+++	+++	+++	ND	>32	>32
A-39	+	>32	+	+	+	+	ND	+	>32
A-40	+	+	++	++	++	+	ND	>32	+
A-41	++	++	+++	+++	+++	+++	ND	+	++
A-42	++	>32	++	++	++	ND	++	+	>32
A-43	++	>32	++	++	++	++	ND	+	>32
A-44	++	++	++	++	++	++	ND	+	>32
A-45	++	++	++	+++	+++	+++	ND	+	>32
A-46	>32	>32	>32	+	+	>32	ND	>32	>32
A-47	>32	+++	+++	+++	+++	+++	+++	>32	>32
A-48	+	>32	>32	+++	+++	+++	ND	>32	>32
A-49	+++	+++	+++	+++	+++	+++	+++	+	>32
A-50	+++	+++	+++	+++	+++	+++	+++	+	>32

Table B (continued)

Ref.	Organism (Minimum Inhibitory Concentration (MIC), μg/mL)								
	A	B	C	D	E	F	G	H	I
A-51	+++	+++	+++	+++	+++	ND	ND	+++	>32
A-52	+	>32	+++	+++	ND	+++	ND	>32	>32
A-53	+++	>32	+++	+++	+++	+++	+++	>32	>32
A-54	+++	+++	+++	+++	+++	+++	ND	+	>32
A-55	+	++	+	++	++	+	ND	+	>32
A-56	>32	+	+	++	++	++	ND	>32	>32
A-57	+	+++	++	++	++	+	ND	>32	>32
A-58	+	+++	++	+	++	++	ND	+	>32
A-59	+	+++	+++	++	++	+	ND	+	>32
A-60	>32	>32	>32	>32	>32	>32	ND	>32	>32
A-61	>32	+++	>32	>32	>32	>32	ND	>32	>32
A-62	>32	>32	>32	>32	>32	>32	ND	>32	>32
A-63	+	++	++	++	++	++	ND	+	>32
A-64	+	+	+	+	+	+	ND	>32	+
A-65	+	+	+	+	+	+	ND	>32	>32
A-66	>32	>32	>32	>32	>32	>32	ND	>32	>32
A-67	+++	+++	+++	+++	+++	+++	ND	>32	>32
A-68	+++	+++	+++	+++	+++	+++	+++	>32	>32
A-69	>32	>32	>32	>32	>32	>32	ND	>32	>32
A-70	>32	+++	+++	+++	+++	+++	ND	>32	>32
A-71	+++	++	+++	+++	+++	+++	ND	+	+++
A-72	>32	>32	>32	>32	>32	>32	ND	>32	>32
A-73	>32	>32	>32	>32	>32	>32	ND	>32	>32
A-74	+	+	++	++	+	++	ND	+	>32
A-75	+++	>32	+++	+++	+++	+++	ND	+	>32
A-76	+	+	++	+++	+++	++	ND	+	+

[0129] Table C shows additional antibacterial data for selected compounds, against two drug resistant bacterial strains: *E. faecium* (ATCC 51559, VRE) and *S. pneumoniae* (ATCC 51422, PRSP). (MIC values are keyed in the same manner as Table B.)

Table C — Additional Antibacterial Data		
Compound Reference	Organism (Minimum Inhibitory Concentration (MIC), μg/mL)	
	E. faecium (ATCC 51559)	*S. pneumoniae* (ATCC 51422)
A-2	+++	+
A-3	+++	+
A-7	+++	+
A-11	+++	+
A-34	+++	+
A-53	+++	+
A-68	+++	>32

[0130] The foregoing detailed description of the invention includes passages that are chiefly or exclusively concerned with particular parts or aspects of the invention. It is to be understood that this is for clarity and convenience, that a particular feature may be relevant in more than just the passage in which it is disclosed, and that the disclosure herein includes all the appropriate combinations of information found in the different passages. Similarly, although the various figures and descriptions herein relate to specific embodiments of the invention, it is to be understood that where a specific feature is disclosed in the context of a particular figure or embodiment, such feature can also be used, to the extent appropriate, in the context of another figure or embodiment, in combination with another feature, or in the invention in general.

[0131] Further, while the present invention has been particularly described in terms of certain preferred embodiments, the invention is not limited to such preferred embodiments. Rather, the scope of the invention is defined by the appended claims.